

70 ANNI DI REUMATOLOGIA
ALLE MOLINETTE



Torino, 11-12 ottobre 2019



L'Artrite Reattiva Oggi

Quadri clinici e opzioni terapeutiche

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Struttura Complessa Reumatologia

Emerging Euler Network - Social Media Co-Lead

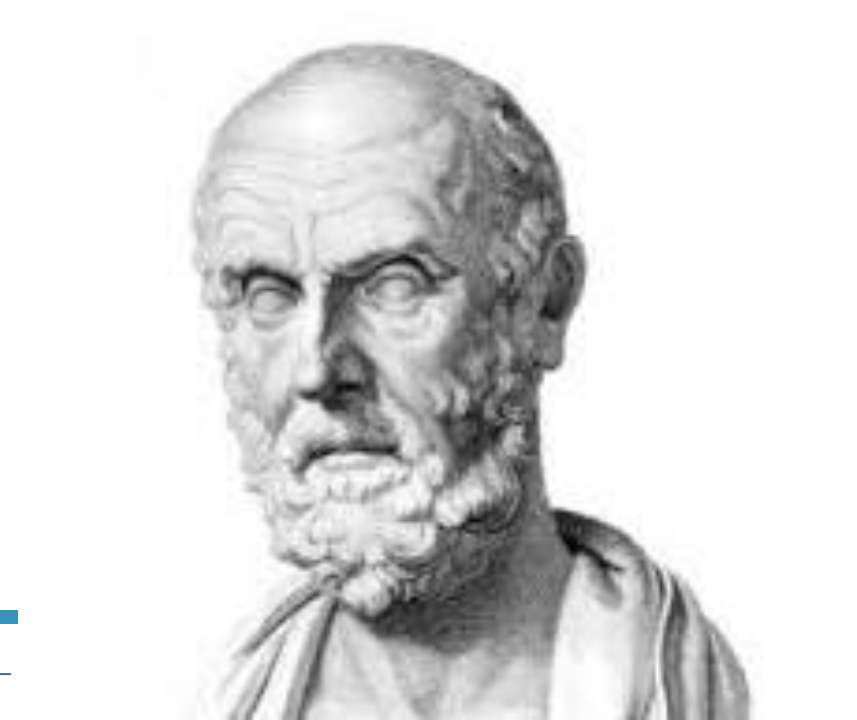
Centro Studi – Società Italiana di Reumatologia





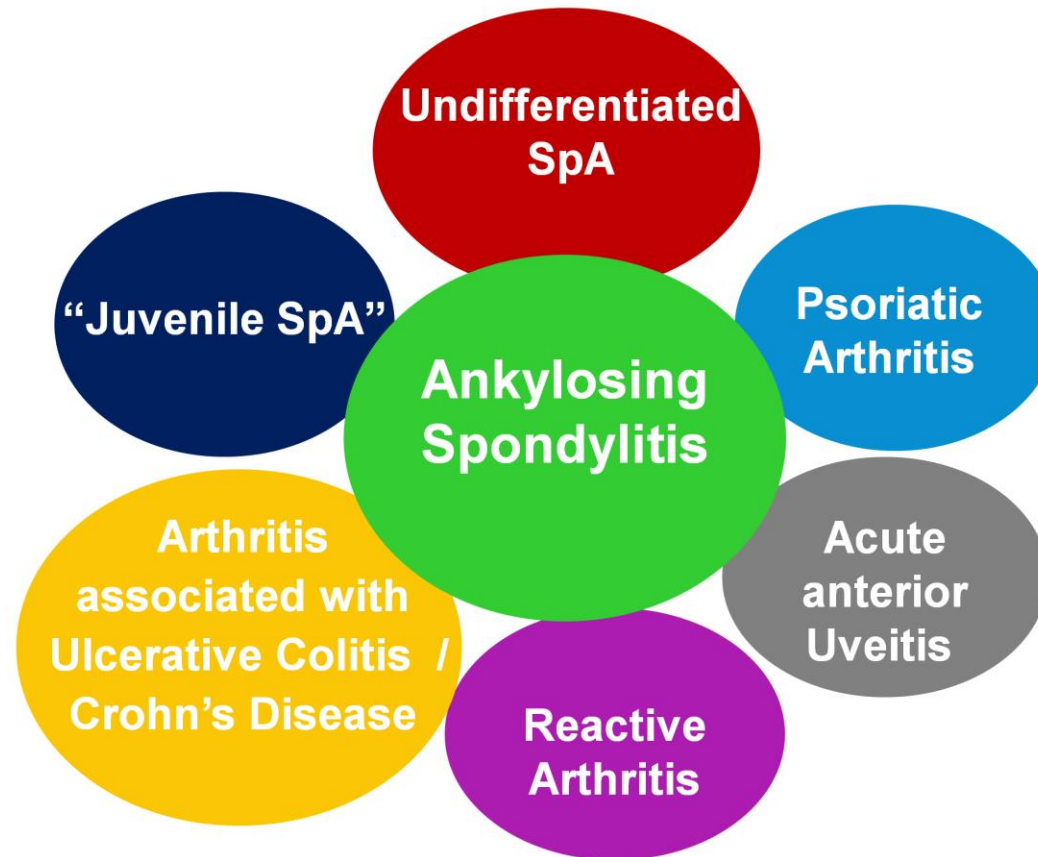
ABBVIE, BALDACCI, BIOGEN,
CELGENE, CHIESI, GRUNENTHAL,
BMS, JANSSEN, NOVARTIS, LILLY,
SANOFI, UCB, MYLAN

SIMONE PARISI



Classificazione

Spondyloarthritides (SpA)

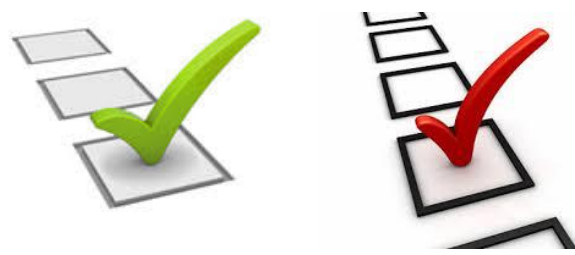


Epidemiologia

- ReA is more common in young adults, 20-40 years of age
- Affects equally men and women when a digestive infection is present, more frequently men when it follows a *Chlamydia trachomatis* infection
- Annual incidence 30/100,000
- Sexually acquired reactive arthritis 3-8%
- *Chlamydiae* are the most common microorganisms (trachomatis 13.6% of cases)
- Infections may be asymptomatic in 10% of cases



Criteria



MAJOR CRITERIA	<ol style="list-style-type: none">1) Arthritis with 2 of 3 of the following findings:<ul style="list-style-type: none">- Asymmetric- Mono or oligoarthritis- Lower limbs involvement2) Preceding symptomatic infection with 1 or 2 of the following findings:<ul style="list-style-type: none">- Enteritis (defined as diarrhea for at least 1 day, 3 days to 6 weeks before the onset of arthritis)- Urethritis (dysuria or discharge for at least 1 day, 3 days to 6 weeks before the onset of arthritis)
MINOR CRITERIA	<p>At least one of the following:</p> <ol style="list-style-type: none">1. Evidence of triggering infection:<ul style="list-style-type: none">- Positive urine ligase reaction or urethral/cervical swab for Chlamydia Trachomatis- Positive stool culture for enteric pathogens associated with reactive arthritis2. Evidence of persistent synovial infection (positive immunohistology or PCR for Chlamydia)

Agenti eziologici

- Infezioni gastrointestinali

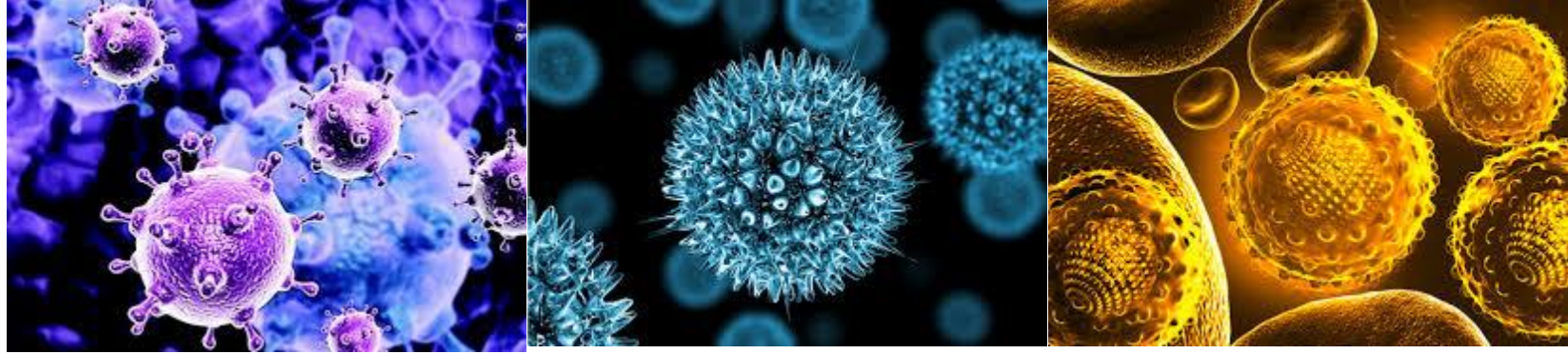
- *Salmonella* of various serovars
- *Shigella*, especially *Shigella flexneri*, but also *Shigella dysenteriae* and *Shigella sonnei*
- *Yersinia*, including *Yersinia enterocolitica* 0:3 and 0:9 and *Yersinia pseudotuberculosis*
- *Campylobacter*, especially *Campylobacter jejuni*
- *Clostridium difficile*

- Infezioni genitourinarie

- *Chlamydia trachomatis*

- Altre

- *Chlamydia pneumoniae*, *Escherichia coli*, *Ureaplasma urealyticum*, and *Mycoplasma genitalium*.
- Intravesical *Bacillus Calmette-Guerin* (BCG)
- *Human immunodeficiency virus* (HIV) infection





Eziopatogenesi

ReA manifests approximately **1 to 3 weeks after an infection**, but the mechanisms of interaction between the microbial antigen and the host remain unknown.

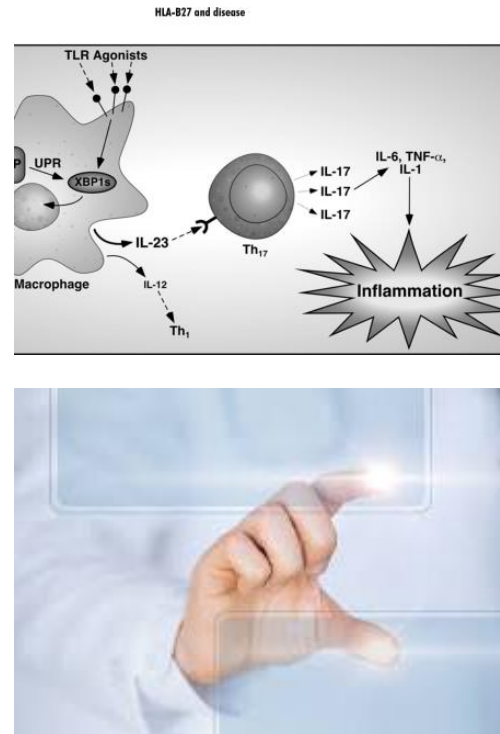
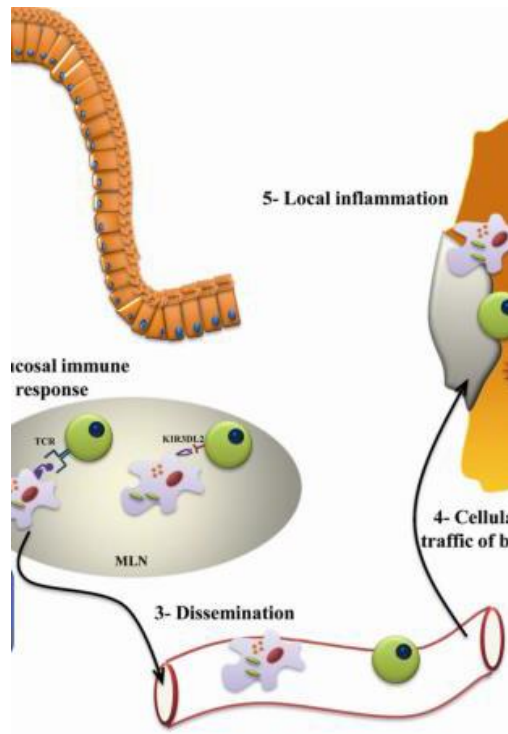
Synovial fluid cultures are negative, suggesting that reactive arthritis is caused by an over-stimulated autoimmune response or by bacterial antigens which deposit in the joints.

The antigens that trigger reactive arthritis are **Gram-negative intracellular aerobic bacteria**. These first invade a mucosal site that can be gastrointestinal (enteric pathogens) or urogenital.

The altered immune response leads to the **unbalanced production of Th2 cytokines**, and this further helps the **poor elimination of the antigen by the host**.

The presence of the HLA-B27 gene does not seem to be related to the onset of reactive arthritis but to its **perpetuation into a chronic form**, and one hypothesis is that this haplotype favors the **cross-reaction** between antigen and host, or might be itself a target of the immune response.

Eziopatogenesi – HLAB27

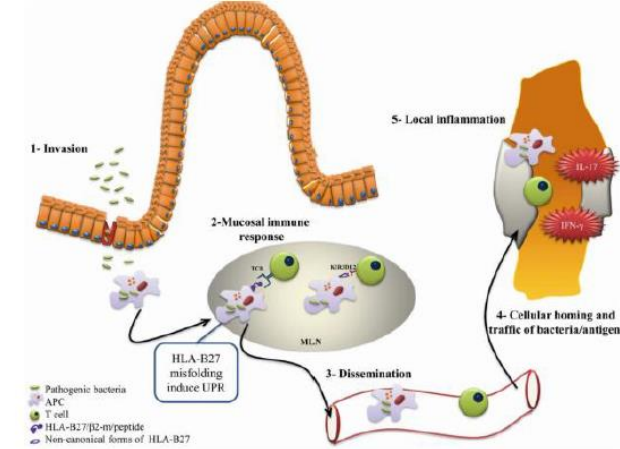


HLA-B27 is positive in **50% to 80%** of patients with reactive arthritis.

Several hypotheses have evolved to explain the role of HLA-B27 in these processes.

The HLA-B27 misfolding hypothesis observes that **HLA-B27 folds** more slowly than other HLA types as it is assembled in the endoplasmic reticulum. This slow pace is felt to lead to improper folding and instability of HLA-B27, **with accumulation of HLA-B27 homodimers and beta-2 microglobulin, with activation of inflammatory processes.**

Eziopatogenesi – HLAB27



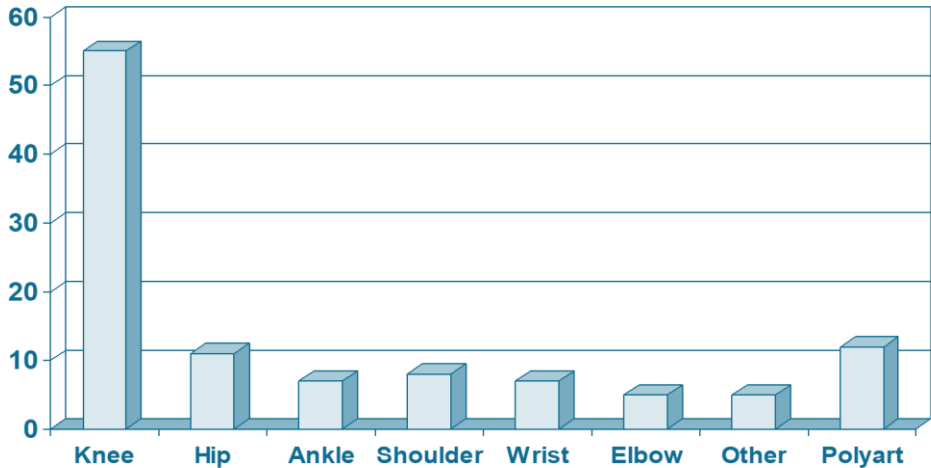
- The arthritogenic peptide hypothesis relies on aberrant antigen presentation in pathogenesis. It states that microbial peptides mimic certain self-peptides, causing reactivity of HLA-B27 specific, CD8 bearing cytotoxic T lymphocytes. It is suggested that this then leads to autoimmunity and inflammation with tissue damage.
- Because some patients who are HLA-B27 negative also develop reactive arthritis, other investigations have focused on the role of microbial factors in pathogenesis. One recent study of patients with reactive arthritis due to *S. typhimurium* suggests that Salmonella outer membrane protein is able to stimulate interleukin (IL)-17/IL-23 production in synovial immune cells, possibly contributing to arthropathy.
- Altered Microbiota



Clinica

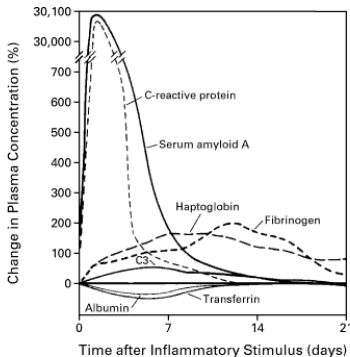
- ***MSK symptoms***
 - Arthritis
 - Enthesitis
 - Dactylitis
 - Low back pain
- ***Extraarticular manifestations***
 - Conjunctivitis
 - Genitourinary tract symptoms
 - Oral lesions, including mucosal ulcers
 - Cutaneous eruptions and other skin changes, such as keratoderma blennorrhagica (hyperkeratotic skin lesions on soles and palms) and erythema nodosum
 - Onychopathy
 - Genital lesions such as circinate balanitis

Clinica - Diagnosi

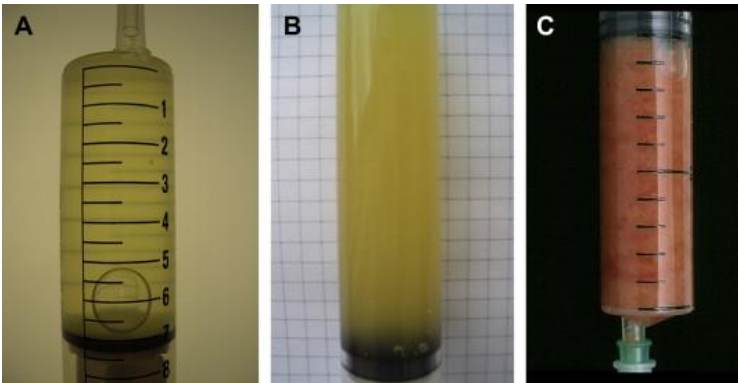


Laboratory

WBC – White Blood Count
 ESR – erytrosedimentation rate
 CRP – C-reactive protein
 PCT – procalcitonin



Chlamydial/nonChlamydial



Synovial Fluid Analysis

	WBC/mm ³	Color	Viscosity
Normal	< 150	Colorless/Straw	High
Noninflammatory	< 3,000	Straw/Yellow	High
Inflammatory	> 3,000	Yellow	Low
Septic (purulent)	> 50,000	Pus/Mixed	Mixed
Hemorrhagic	Similar to blood	Red	Low



Differential Diagnosis

- Septic arthritis (inflammatory monoarthritis or oligoarthritis)
- Disseminated gonococcal infection (genitourinary symptoms, arthritis, Achille's tenosynovitis, febbre, leucocitosi)
- Enteroviral infection by Coxsackie and Echovirus (diarrhea, arthritis)
- Whipple's disease (acute oligoarthritis or chronic polyarthritis)
- Inflammatory bowel disease (diarrhea, arthritis)
- Behçets disease (diarrhea, arthritis, skin and genital ulcers, rash, uveitis)
- Crystalline arthropathy
- Lyme disease
- Poststreptococcal arthritis

Management



Author, year (ref.)	No. of patients	Anti-TNF α agent/mg per kg	Clinical evidence of preceding infection	Biologic evidence of preceding infection	Severe adverse effect	Efficacy
Flagg et al, 2005 (10)	7	E	At least clinical or biologic evidence within 6 weeks before the onset of arthritis	At least clinical or biologic evidence within 6 weeks before the onset of arthritis	None	56%†
Kaipiainen-Seppanen et al, 2003 (11)	2	I/3	Diarrhea/none	<i>Yersinia enterocolitica</i> (serology)	None	Yes
Gaylis, 2003 (12)	1	I/5	HIV	HIV	None	Yes
Gill and Majithia, 2008 (13)	1	I/3	Urethritis	None	None	Yes
Schafrański, 2010 (14)	1	I/5	Urethritis	<i>Chlamydia trachomatis</i>	None	Yes
Abdelmoula et al, 2008 (15)	1	I/3	None	<i>C trachomatis</i> (serology and DNA in the joint)	None	Yes
Present study	10	I, A, E	Clinical evidence within the month before the onset of arthritis	Biologic evidence within the month before the onset of arthritis	None	90%

* HIV = human immunodeficiency virus (see Table 1 for other definitions).

† Both in reactive arthritis and in undifferentiated arthritis.

Management

Acute

Chronic

FANS

CS-DMARD

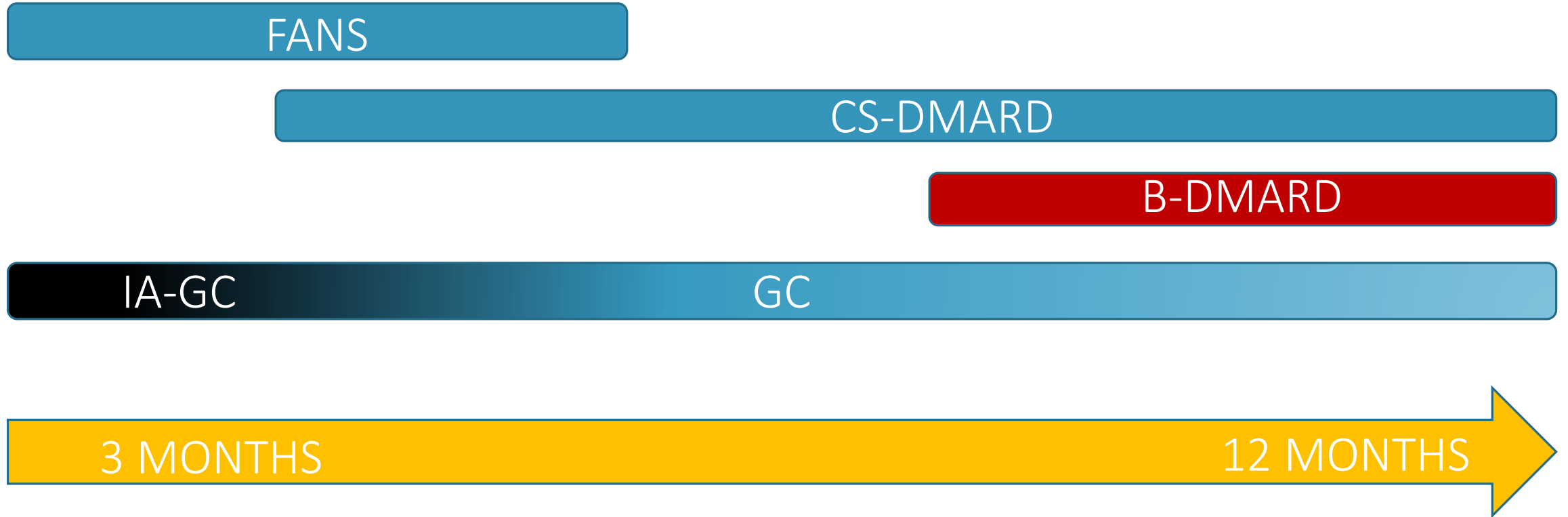
B-DMARD

IA-GC

GC

3 MONTHS

12 MONTHS



Prognosis

HLA-B27 positive patients had more a severe acute disease course with a longer duration of symptoms, more extraarticular symptoms, and more chronic symptoms.

- ReA Usually self-limiting
- Duration 3 to 12 months
- 25-50% flare and require re-treatment
- 25-30% can become chronic in 30% of cases

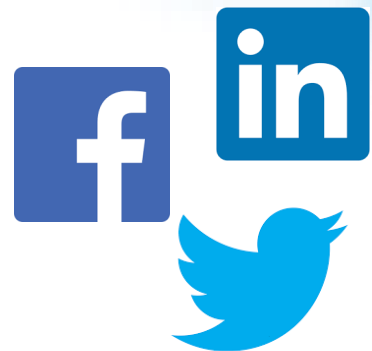
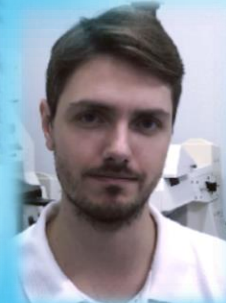


CONCLUSION

- ReA affects equally men and women when a digestive infection is present, more frequently men when it follows a *Chlamydia trachomatis* infection
- *Chlamydiae* are the most common microorganisms (trachomatis 13.6% of cases)
- Infections may be asymptomatic in 10% of cases
- ReA can become chronic in 30% of cases but usually self-limiting
- Duration 3 to 12 months
- HLA-B27 has been associated with a more severe disease course and also more frequent chronic disease



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